REMARKS

Claim Amendments

Claims 3-4 and 9-14 have been cancelled.

Claims 1, 2, 5 and 6 have been amended to remove the phrase "such as a human" as not being appropriate under U.S. practice.

Claims 5 and 6 have also been amended to direct the treatment of a solid tumour cancer more specifically toward the treatment of colorectal cancer, which treatment is supported by the specification disclosure, *e.g.*, by the comparative demonstration at pages 16-19, and which treatment the Examiner has acknowledged is enabled by the specification (Action at page 3).

Claims 1, 2, 5 and 6 have also been amended to be directed toward the simultaneous administration of AZD2171 and ZD6126. In context of chemotherapy and the specification disclosure as a whole, "simultaneous administration" will be understood by the skilled person to mean that the patient is undergoing AZD2171 chemotherapy at the same time the patient is undergoing ZD6126 chemotherapy, as opposed to sequential therapy where one therapy is completed before the other is started. Thus "simultaneous" would not require that the dose of one agent is given to the patient at the same time as the dose of the other, provided that the therapies were overlapping. The skilled person would also understand, particularly with the guidance of, *e.g.*, the comparative demonstration at pages 16 to 19 and Figure 1, that the presently amended claims would encompass the "concurrent schedule," where the AZD2171 and ZD6126 therapies were both given for days 0-2 and the AZD2171 therapy thereafter continued alone until day 14, inasmuch as both therapies were given simultaneously for days 0-2.

These claims amendments are being made without disclaimer or prejudice to Applicant's right to prosecute any subject matter thereby deleted in one or more continuing applications. Following entry of the above amendments, claims 1-2 and 5-8 remain pending in this application.

Rejection and Objection to Specification and Claims Based on Spelling

At page 2 of the Action the Examiner has objected to the specification and claims for allegedly not complying with 35 U.S.C. § 112, as not being "clear, concise and exact" in that *British* English spelling is used throughout rather than *American* English spelling. This objection is respectfully traversed. As specifically recognized by §608.01 of the MPEP, 37 CFR 1.52(b)(1)(ii) only requires the application to be in the English language, and there is no additional requirement that the English must be American English:

> Examiners should not object to the specification and/or claims in patent applications merely because applicants are using British English spellings (e.g., colour) rather than American English spellings. It is not necessary to replace the British English spellings with the equivalent American English spellings in the U.S. patent applications. Note that 37 CFR 1.52(b)(1)(ii) only requires the application to be in the English language. There is no additional requirement that the English must be American English.

(MPEP §608.01, 8th Edition, Rev. 6, August 2007).

It is therefore respectfully requested that these objections and/or rejections based on the British English spelling be withdrawn.

Claim Rejections - 35 USC § 112, 1st Paragraph

Beginning at page 3 of the specification, claims 3-6 are rejected under 35 U.S.C. 112, first paragraph, "because the specification, while being enabling for treating colorectal cancer, does not reasonably provide enablement for 'treating cancer'." Specifically, the Examiner asserts that "the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims."

While Applicant does not agree with the Examiner's assertion, claims 3 and 4 have been cancelled and claims 5 and 6 have been amended above to be specifically directed toward "the treatment of colorectal cancer." This ground for rejection therefore has been overcome and it is respectfully requested that it now be withdrawn.

Claim Rejections - 35 USC § 112, 2nd Paragraph

Claims 9-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner notes that claims 9-14 provide for the use of AZD2171 and ZD6126, but do not set forth any steps involved in the method/process. This ground for rejection has been obviated by the above cancellation of claims 9-14.

Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite with respect to the phrase "such as." This ground for rejection has been overcome by the amendments to claims 1, 2, 5 and 6 (claims 3-4 having been cancelled), whereby the phrase "such as a human" has been removed from each claim.

Claim Rejections - 35 USC § 101

The rejection of claims 9-14 under 35 U.S.C. 101 as being in a "use" format has been obviated by the cancellation of these claims.

Claim Rejections - 35 USC § 103

Claim 1-8 are rejected under 35 USC 103(a) based on two combinations of references:

- Beginning at page 9 of the Action, claims 1-8 are rejected as being unpatentable over US 2003/0055024 (US '024) in view of WO 01/74360 (WO '360)[1] and US 6,420,335 (US '335).
- Beginning at page 11 of the Action, claims 1-8 are rejected as being unpatentable over US 2003/0055024 (US '024) in view of WO 00/47212 (WO '212)[2] and US 6,420,335 (US '335).

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[1] The Examiner's attention is called to US National Stage application 10/240,413 of Applicant's assignee, corresponding to WO 01/74360, which US application is currently pending before Examiner Charlesworth E. Rae in Group Art Unit 1611, in which a non-final action has been mailed.

[2] The Examiner's attention is called to the fact that US Patent 7,074,800 issued to Applicant's assignee on July 11, 2006 based on the US National Stage application corresponding to WO 00/47212; and continuing application 11/169,122 is currently pending before Examiner Tamthom Ngo Truong in Group Art Unit 1624, with a first Action predicted in three months from the present date.

In addition, Applicant wishes to point out that the present specification itself discusses the present invention in context of what might be considered to be even more pertinent prior art than that applied by the Examiner. This will also be discussed below.

In any event, whether or not one might consider any of these combinations of prior art references to give rise to *prima facie* obviousness, it is respectfully submitted that any such *prima facie* obviousness is overcome by the unexpected and significantly improved results achieved by the combination therapy as now claimed, as demonstrated at pages 16-19 of the specification, graphically illustrated in Figure 1 and discussed below at pages 11-12.

Examiner's Obviousness Rejection Over US '024 in View of WO '360 and US '335

US '024 is said "to discloses the use of a vascular-damaging agent (i.e., an antiangiogenic, in particular ZD6126) in the manufacture of a medicament for administration in divided doses, optionally with a pharmaceutically acceptable excipient or carrier (¶ 0017-20), for the use in the production of a vascular-damaging effect in a human (abstract) particularly a method for the treatment of a cancer involving a solid tumor (¶ 0001)." The Examiner acknowledges that this reference "does not expressly disclose administering together with AZD2171 and/or ionizing radiation." The Examiner therefore cites WO '360 as disclosing 4-(4-fluoro-2-methylindo1-5-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-yl) propoxy) quinazoline (i.e., AZD2171) as a preferred antiangiogenic (noting page 16, lines 15-24, and page 24, lines 6 and 20), and also US '335 as disclosing combination therapy using ionizing radiation and antiangiogenic factors (pointing to the claims and Brief Summary).

US '024, US '335 and WO '360 are said to be analogous art "because they are from the same field of endeavor viz treating cancer with the combination of anticancer methods involving antiangiogenic compounds."

The Examiner concludes that it would be *prima facie* obvious to combine these references on the generalized assertion that "it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. In this case, AZD2171 and ZD 6126 are said to be "equivalents in that they are both antiangiogenic compounds used to treat certain cancers." Applicant respectfully disagrees with the

applicability of this generalization to the particular circumstances of the presently claimed invention, where the combination is of antiangiogenic agent and a vascular targeting agent. Nevertheless, any such *prima facie* obviousness that might be said to arise from these references is overcome by the unexpected and significantly improved results achieved by the combination therapy as now claimed, as demonstrated at pages 16-19 of the specification, graphically illustrated in Figure 1, and discussed further below at pages 11-12.

Examiner's Obviousness Rejection Over US '024 in View of WO '212 and US '335

Claims 1-8 are also rejected under 35 USC 103(a) as being unpatentable over US 2003/0055024 (US '024) in view of WO 00/47212 (WO '212) and US 6,420,335 (US '335).

US '024 is said to disclose "the use of a vascular-damaging agent (i.e., an antiangiogenic, in particular ZD6126) in the manufacture of a medicament for administration in divided doses, optionally with a pharmaceutically acceptable excipient or carrier (¶ 0017-20), for the use in the production of a vascular-damaging effect in a human (abstract) particularly a method for the treatment of a cancer involving a solid tumor (¶ 0001)." The Examiner acknowledges that US '024 "does not expressly disclose administering ZD6126 together with AZD2171 and/or ionizing radiation."

The Examiner therefore cites WO '212 as disclosing 4-(4-fluoro-2-methylindo1-5-yloxy)-6-methoxy-7-(3-(pyrrolid in-1-y1) propoxy) quinazoline (i.e., AZD2171) as an antiangiogenic (claims 1, 9 and 18 and 21-22), and US '335 as disclosing combination therapy using ionizing radiation and antiangiogenic factors (pointing to the claims and Brief Summary).

WO '024, US '335 and WO '212 are said to be analogous art "because they are from the same field of endeavor viz treating cancer with the combination of anticancer methods involving antiangiogenic compounds."

The Examiner asserts that it would be *prima facie* obvious to combine these references on the generalized assertion that "it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose." In this case,

AZD2171 and ZD 6126 are said to be "equivalents in that they are both antiangiogenic compounds used to treat certain cancers."

Applicant respectfully disagrees with the applicability of this generalization to the particular circumstances of the presently claimed invention, where the combination is of antiangiogenic agent and a vascular targeting agent. Nevertheless, any such *prima facie* obviousness that might be said to arise from these references is overcome by the unexpected and significantly improved results achieved by the combination therapy as now claimed, as demonstrated at pages 16-19 of the specification, graphically illustrated in Figure 1, and discussed further below at pages 11-12.

Discussion of Prior Art in the Present Application

The presently claimed invention is directed toward a method for the production of an antiangiogenic and/or vascular permeability reducing effect, and also specifically toward a method for the treatment of colorectal cancer, by the simultaneous administration of an effective amount of AZD 2171 with an effective amount of ZD6126, optionally before, after or simultaneously with an effective amount of ionising radiation. Claim 7 is directed toward a pharmaceutical composition which comprises AZD 2171 and ZD6126, and claim 8 is directed toward a kit which comprises AZD 2171 and ZD6126.[3]

The position of the presently claimed invention in the context of what is believed to be the most pertinent prior art is presented in the present specification at pages 3-5. This presentation begins with a discussion of WO '212, which discloses a genus of quinazoline derivatives possessing activity against VEGF receptor tyrosine kinase (VEGF RTK), and thus produce antiangiogenic and/or vascular permeability reducing effects in warm-blooded animals. Such an antiangiogenic agent inhibits the formation of new vasculature that is essential, *e.g.*, to tumour growth. The present specification points out that AZD2171 falls within the genus of the WO '212 quinazoline derivatives, and is the compound of Example 240 of WO '212.

[3] It should be understood throughout this discussion that either or both agents may be in the form of a pharmaceutically acceptable salt.

At page 3, beginning at line 14, the present specification also points out that WO '212 states that compounds of that invention:

> ... may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment.

The present specification further notes that WO '212 describes examples of such conjoint treatment including surgery, radiotherapy and various types of chemotherapeutic agent including inhibitors of growth factor function and the vascular damaging agents described in WO 99/02166 (WO '166),[4] such as N-acetylcolchinol-O-phosphate, which is ZD6126.

However, nowhere in WO '212 is the specific combination of AZD2171 and ZD6126 suggested. Moreover, nowhere in WO '212 does it state that use of any compound of the WO '212 invention with other treatments will produce surprisingly beneficial effects.

The present specification beginning at page 3, line 28, then goes on to discuss the vascular damaging agents of WO '166. Whereas antiangiogenic agents inhibit the formation of neovascularization, vascular damaging agents can cause a reversal of neovascularisation by damaging the newly-formed vascular endothelium. It is noted that WO '166 describes tricyclic compounds that surprisingly have a selective damaging effect on newly formed vasculature as compared to the normal, established vascular endothelium of the host species, and that this is a property of value in the treatment of disease states associated with angiogenesis including cancer. Compounds which damage newly formed vasculature are vascular targeting agents (VTAs) and are also known as vascular damaging agents (VDAs).

The present specification points out at page 4, line 12 through the middle of page 5, that one such compound described in WO '166 is N-acetylcolchinol-O-phosphate, the compound of Example 1 of WO '166, which is ZD6126. The present specification goes on to note that WO '166 states that:

> ... compounds of the invention may be administered as sole therapy or in combination with other treatments. For the treatment of solid tumours compounds of the invention may be administered in combination with

[4] The Examiner's attention is called to the fact that US Patent 6,423,753 issued to Angiogene Pharmaceuticals on July 23, 2002 based on the US National Stage application corresponding to WO 99/02166. According to PAIR there has been no continuing application.

> radiotherapy or in combination with other anti-tumour substances for example those selected from mitotic inhibitors, for example vinblastine, paclitaxel and docetaxel; alkylating agents, for example cisplatin, carboplatin and cyclophosphamide, antimetabolites, for example 5-fluorouracil, cytosine arabinoside and hydroxyurea; intercalating agents for example adriamycin and bleomycin; enzymes, for example asparaginase; topoisomerase inhibitors for example etoposide, topotecan and irinotecan; thymidylate synthase inhibitors for example raltitrexed; biological response modifers for example interferon; antibodies for example edrecolomab, and anti-hormones for example tamoxifen. Such combination treatment may involve simultaneous or sequential application of the individual components of the treatment.

However, the present specification correctly observes in the middle of page 5 that nowhere in WO '166 is the specific combination of ZD6126 and AZD2171 suggested, and that nowhere in WO '166 does it state that use of any compound of the invention therein with other treatments will produce surprisingly beneficial effects.

Unexpected Significantly Improved Beneficial Effects of the Presently Claimed Invention

The present specification then goes on to state *with respect to the present invention* that:

> Unexpectedly and surprisingly we have now found that the particular compound AZD2171 used in combination with a particular selection from the broad description of combination therapies listed in WO 00/47212, namely with ZD6126, produces significantly better effects than any one of AZD2171 and ZD6126 used alone. In particular, AZD2171 used in combination with ZD6126 produces significantly better effects on solid tumours than any one of AZD2171 and ZD6126 used alone.

It is respectfully submitted that *the most surprising and significant beneficial effects* on solid tumours are realized with the *simultaneous administration* of AZD2171 and ZD6126 *as now claimed*, which is clearly demonstrated by the "concurrent schedule" of treatment described at pages 16-19 of the present specification, tabulated on Table 1, and graphically illustrated in Figure 1.

Table 1 at page 18 of the present specification tabulates the comparison of "Mean % Inhibition of tumour growth at day 14" and the "Number of tumour regressions evident at day 14" for each of four treatment schedules.

- In the first treatment schedule AZD2171 was dosed alone on each of days 0 - 14, and achieved a Mean % Inhibition of tumour growth at day 14 of 62%, but *none* of the 9 tumours evidenced regression at day 14.
- In the second treatment schedule ZD6126 was dosed alone on each of days 0 - 2, and achieved a Mean % Inhibition of tumour growth at day 14 of 65%, but *only 1* of the 9 tumours evidenced regression at day 14.
- In the third, *sequential* treatment schedule, ZD6126 was dosed alone on each of days 0 - 2, and AZD2171 was dosed alone on each of days 3 - 14, and achieved a Mean % Inhibition of tumour growth at day 14 of 96%, and 2 of the 9 tumours evidenced regression at day 14.
- In contrast to the other treatment schedules, in the fourth, *concurrent* treatment schedule, AZD2171 was *simultaneously* dosed with ZD6126 for days 0 - 2 followed by the continued dosing of AZD2171 for the remainder of the 14 days, and this treatment schedule resulted in *160% Mean % Inhibition* of tumour growth at day 14 (that is, *total inhibition of tumour growth plus 60% regression*), and *all 9 tumours* evidenced regression.

These results are graphically depicted in Figure 1 where the results of the *concurrent treatment schedule* is depicted by the *bottom line*, very clearly showing total tumour growth inhibition and significantly better tumour regression initially (during the period of simultaneous dosing) and continuing throughout the 14 day period, even relative to the sequential treatment schedule, which itself is significantly better after 14 days than the treatment schedules in which AZD2171 and ZD6126 are dosed alone.

It is respectfully submitted that any *prima facie* obviousness that might be said to arise from the disclosures of WO '212 and WO '166, either alone or in combination, is overcome by this demonstration of the unexpected, significantly improved tumour inhibition *and regression* when the AZD2171 and ZD6126 therapies are administered simultaneously, as presently claimed.

It is not seen that the particular combinations of prior art references used by the Examiner in formulating his obviousness rejections are any more material that the prior art

already acknowledged in the present specification and summarized above. Nevertheless, any *prima facie* obviousness that the Examiner asserts arises from the prior art combinations applied to the obviousness rejections is also overcome by the surprising and unexpected beneficial results of the presently claimed invention as demonstrated in the present specification as discussed above.

Conclusion

All grounds for objection and/or rejection having been addressed and obviated or overcome by the above amendments and or arguments, it is believed that all claims now pending in this application are in condition for allowance. Therefore, withdrawal of all objections and grounds for rejection and the allowance of this application are respectfully requested

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: **April 15, 2008** By: _____

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